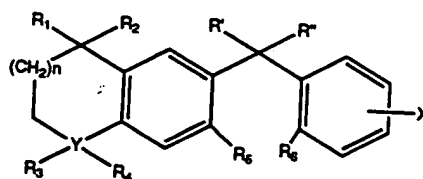
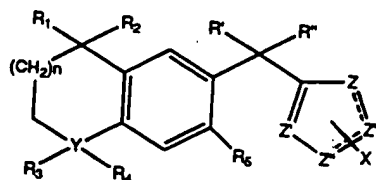


We claim:

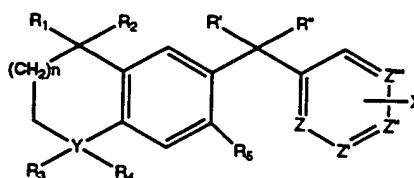
1. A ligand which selectively activates Retinoid X Receptors in preference to Retinoic Acid Receptors.
2. A ligand which modulates a process selectively mediated by Retinoid X Receptors in preference to Retinoic Acid Receptors.
3. The ligand of claim 1 wherein said ligand is at least five-fold more potent an activator of Retinoid X Receptors than of Retinoic Acid Receptors.
4. The ligand of claim 3 wherein said ligand has an efficacy of less than 20% for Retinoic Acid Receptors.
5. A compound having the formula:



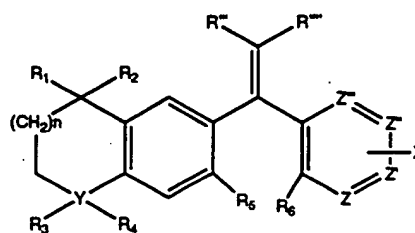
OR



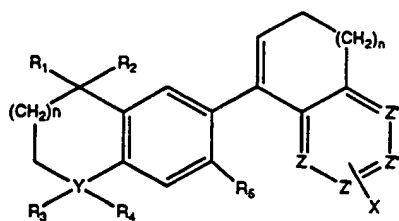
OR



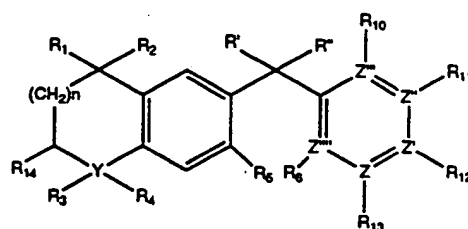
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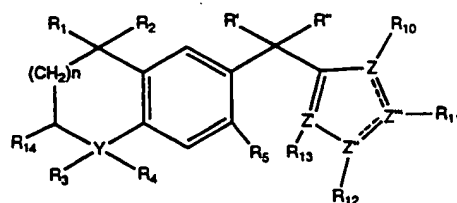
or



or



or



wherein

$R_1$  and  $R_2$ , each independently, represent hydrogen or lower alkyl or acyl having 1-4 carbon atoms;

Y represents C, O, S, N, CHOH, CO, SO, SO<sub>2</sub>, or a  
5 pharmaceutically acceptable salt;

$R_3$  represents hydrogen or lower alkyl having 1-4 carbon atoms where Y is C or N;

$R_4$  represents hydrogen or lower alkyl having 1-4 carbon atoms where Y is C, but  $R_4$  does not exist if Y is N, and neither  $R_3$  or  $R_4$   
10 exist if Y is S, O, CHOH, CO, SO, or SO<sub>2</sub>;

$R'$  and  $R''$  represent hydrogen, lower alkyl or acyl having 1-4 carbon atoms, OH, alkoxy having 1-4 carbon atoms, thiol or thio ether, or amino,

or  $R'$  or  $R''$  taken together form an oxo (keto), methano,  
15 thioketo, HO-N=, NC-N=, ( $R_7R_8$ )N-N=, epoxy, cyclopropyl, or cycloalkyl group and wherein the epoxy, cyclopropyl, and cycloalkyl groups can be substituted with lower alkyl having 1-4 carbons or halogen;

$R'''$  and  $R''''$  represent hydrogen, halogen, lower alkyl or acyl  
20 having 1-4 carbon atoms,

or  $R'''$  and  $R''''$  taken together form a cycloalkyl group having 3-10 carbons, and wherein the cycloalkyl group can be substituted with lower alkyl having 1-4 carbons or halogen;

$R_5$  represents hydrogen, a lower alkyl having 1-4 carbons,  
25 halogen, nitro, OR<sub>7</sub>, SR<sub>7</sub>, NR<sub>7</sub>R<sub>8</sub>, or (CF)<sub>n</sub>CF<sub>3</sub>, but  $R_5$  cannot be hydrogen if together  $R_6$ ,  $R_{10}$ ,  $R_{11}$ ,  $R_{12}$  and  $R_{13}$  are all hydrogen and Z, Z', Z'', Z''', or Z'''' are all carbon;

$R_6$ ,  $R_{10}$ ,  $R_{11}$ ,  $R_{12}$ ,  $R_{13}$  each independently represent hydrogen, a lower alkyl having 1-4 carbons, halogen, nitro, OR<sub>7</sub>, SR<sub>7</sub>, NR<sub>7</sub>R<sub>8</sub> or

(CF)<sub>n</sub>CF<sub>3</sub>, and exist only if the Z, Z', Z'', Z''', or Z'''' from which it originates is C, or each independently represent hydrogen or a lower alkyl having 1-4 carbons if the Z, Z', Z'', Z''', or Z'''' from which it originates is N, and where one of R<sub>6</sub>, R<sub>10</sub>, R<sub>11</sub>, R<sub>12</sub> or R<sub>13</sub> is  
5 X;

R<sub>7</sub> represents hydrogen or a lower alkyl having 1-6 carbons;

R<sub>8</sub> represents hydrogen or a lower alkyl having 1-6 carbons;

R<sub>14</sub> represents hydrogen, a lower alkyl having 1-4 carbons, oxo, hydroxy, acyl having 1-4 carbons, halogen, thiol, or thioketone;

10 X is COOH, tetrazole, PO<sub>3</sub>H, SO<sub>3</sub>H, CHO, CH<sub>2</sub>OH, CONH<sub>2</sub>, COSH, COOR<sub>9</sub>, COSR<sub>9</sub>, CONHR<sub>9</sub>, or COOW where R<sub>9</sub> represents a lower alkyl having 1-4 carbons, phenyl, aromatic alkyl, or q-hydroxyphenyl, q-bromophenyl, q-chlorophenyl, q-florophenyl, or q-iodophenyl, where q=2-4, where W is a pharmaceutically acceptable salt, and  
15 where X can originate from any C or N on the ring;

Z, Z', Z'', Z''' and Z''', each independently, represent C, S, O, N, or a pharmaceutically acceptable salt, but is not O or S if attached by a double bond to another such Z or if attached to another such Z which is O or S, and is not N if attached by a  
20 single bond to another such Z which is N;

n = 0-3; and

the dashed lines in the second and seventh structures shown depict optional double bonds.

6. A compound of claim 5 wherein said compound  
25 selectively activates Retinoid X Receptors in preference to Retinoic Acid Receptors.

7. A compound selected from the group consisting of 4-[(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)carbonyl]benzoic acid,

4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)ethenyl]benzoic acid,

4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)cyclopropyl]benzoic acid,

5 4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)ethenyl]benzenetetrazole,

2-[1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)ethenyl]pyridine-5-carboxylic acid,

10 2-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)ethenyl]pyridine-5-carboxylic acid,

ethyl 2-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)ethenyl]pyridine-5-carboxylate,

5-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)ethenyl]pyridine-2-carboxylic acid,

15 2-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)cyclopropyl]pyridine-5-carboxylic acid,

methyl 2-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)cyclopropyl]pyridine-5-carboxylate, and

20 4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)ethenyl]-N-(4-hydroxyphenyl)benzamide.

8. 4-[1-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)ethenyl]benzoic acid.

9. 2-[1-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)ethenyl]pyridine-5-carboxylic acid.

25 10. 2-[1-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)cyclopropyl]pyridine-5-carboxylic acid.

11. A pharmaceutical composition comprising in a

pharmaceutically acceptable vehicle suitable for enteral,  
parenteral, or topical administration, one or more compound of  
claim 2.

12. A pharmaceutical composition comprising in a  
5 pharmaceutically acceptable vehicle suitable for enteral,  
parenteral, or topical administration, one or more compound of  
claim 5.

13. A method for modulating a process selectively  
mediated by one or more Retinoid X Receptors, said method  
10 comprising causing said process to be conducted in the presence of  
a ligand which selectively activates one or more said Retinoid X  
Receptors in preference to Retinoic Acid Receptors.

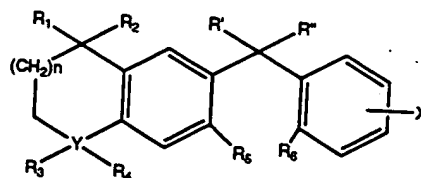
14. The method of claim 13 wherein said ligand is at  
least five-fold more potent an activator of Retinoic Acid Receptors  
15 than of Retinoic Acid Receptors.

15. The method of claim 14 wherein said ligand has an  
efficacy of less than 20% for Retinoic Acid Receptors.

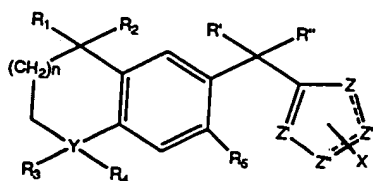
16. A method for modulating a process mediated by one or  
more Retinoid X Receptors, said method comprising causing said  
20 process to be conducted in the presence of at least one ligand as  
set forth in claim 2.

17. A method for modulating a process mediated by one or  
more Retinoid X Receptors, said method comprising causing said  
process to be conducted in the presence of at least one compound as  
25 set forth in claim 5.

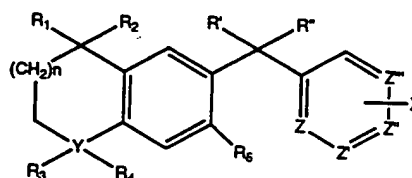
18. A method for modulating a process mediated by one or more Retinoid X Receptors, said method comprising causing said process to be conducted in the presence of at least one compound of the formula:



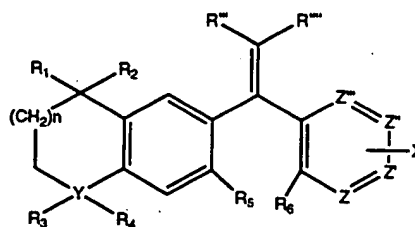
or



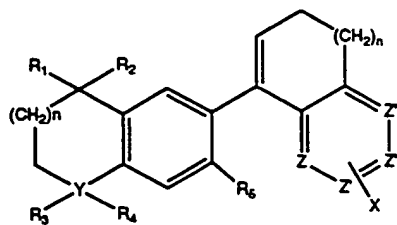
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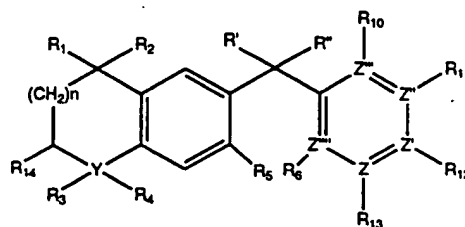
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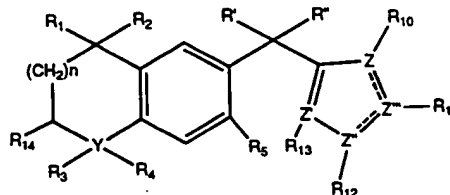
or



or



or



wherein

$R_1$  and  $R_2$ , each independently, represent hydrogen or lower  
5 alkyl or acyl having 1-4 carbon atoms;

$Y$  represents C, O, S, N, CHOH, CO, SO, SO<sub>2</sub>, or a  
pharmaceutically acceptable salt;

$R_3$  represents hydrogen or lower alkyl having 1-4 carbon atoms  
where  $Y$  is C or N;

10  $R_4$  represents hydrogen or lower alkyl having 1-4 carbon atoms  
where  $Y$  is C, but  $R_4$  does not exist if  $Y$  is N, and neither  $R_3$  or  $R_4$   
exist if  $Y$  is S, O, CHOH, CO, SO, or SO<sub>2</sub>;

$R'$  and  $R''$  represent hydrogen, lower alkyl or acyl having 1-4  
carbon atoms, OH, alkoxy having 1-4 carbon atoms, thiol or thio  
15 ether, or amino,



or R' or R'' taken together form an oxo (keto), methano, thioketo, HO-N=, NC-N=, (R<sub>7</sub>R<sub>8</sub>)N-N=, epoxy, cyclopropyl, or cycloalkyl group and wherein the epoxy, cyclopropyl, and cycloalkyl groups can be substituted with lower alkyl having 1-4 carbons or  
5 halogen;

R' " and R'' " represent hydrogen, halogen, lower alkyl or acyl having 1-4 carbon atoms,

or R' " and R'' " taken together form a cycloalkyl group having 3-10 carbons, and wherein the cycloalkyl group can be substituted  
10 with lower alkyl having 1-4 carbons or halogen;

R<sub>5</sub> represents hydrogen, a lower alkyl having 1-4 carbons, halogen, nitro, OR<sub>7</sub>, SR<sub>7</sub>, NR<sub>7</sub>R<sub>8</sub>, or (CF)<sub>n</sub>CF<sub>3</sub>, but R<sub>5</sub> cannot be hydrogen if together R<sub>6</sub>, R<sub>10</sub>, R<sub>11</sub>, R<sub>12</sub> and R<sub>13</sub> are all hydrogen and Z, Z', Z'', Z' ", or Z'' " are all carbon;

R<sub>6</sub>, R<sub>10</sub>, R<sub>11</sub>, R<sub>12</sub>, R<sub>13</sub> each independently represent hydrogen, a  
15 lower alkyl having 1-4 carbons, halogen, nitro, OR<sub>7</sub>, SR<sub>7</sub>, NR<sub>7</sub>R<sub>8</sub> or (CF)<sub>n</sub>CF<sub>3</sub>, and exist only if the Z, Z', Z'', Z' ", or Z'' " from which it originates is C, or each independently represent hydrogen or a lower alkyl having 1-4 carbons if the Z, Z', Z'', Z' ", or Z'' " from  
20 which it originates is N, and where one of R<sub>6</sub>, R<sub>10</sub>, R<sub>11</sub>, R<sub>12</sub> or R<sub>13</sub> is X;

R<sub>7</sub> represents hydrogen or a lower alkyl having 1-6 carbons;

R<sub>8</sub> represents hydrogen or a lower alkyl having 1-6 carbons;

R<sub>14</sub> represents hydrogen, a lower alkyl having 1-4 carbons, oxo, hydroxy, acyl having 1-4 carbons, halogen, thiol, or thioketone;  
25

X is COOH, tetrazole, PO<sub>3</sub>H, SO<sub>3</sub>H, CHO, CH<sub>2</sub>OH, CONH<sub>2</sub>, COSH, COOR<sub>9</sub>, COSR<sub>9</sub>, CONHR<sub>9</sub>, or COOW where R<sub>9</sub> represents a lower alkyl having 1-4 carbons, phenyl, aromatic alkyl, or q-hydroxyphenyl, q-bromophenyl, q-chlorophenyl, q-florophenyl, or q-iodophenyl, where  
30 q=2-4, where W is a pharmaceutically acceptable salt, and where X can originate from any C or N on the ring;

Z, Z', Z'', Z''' and Z'''', each independently, represent C, S, O, N, or a pharmaceutically acceptable salt, but is not O or S if attached by a double bond to another such Z or if attached to another such Z which is O or S, and is not N if attached by a single bond to another such Z which is N;

n = 0-3; and

the dashed lines in the second and seventh structures shown depict optional double bonds.

19. A method according to claim 18 wherein said Retinoid X Receptor is Retinoid X Receptor-alpha, Retinoid X Receptor-beta, or Retinoid X Receptor-gamma.

20. A method according to claim 18 wherein said process is the *in vivo* modulation of lipid metabolism, *in vivo* modulation of skin-related processes, *in vivo* modulation of malignant cell development, or *in vivo* modulation of premalignant lesions.

21. A method according to claim 18 wherein said process is *in vitro* cellular growth and differentiation, or *in vivo* limb morphogenesis.

22. A method for modulating a process mediated by one or more Retinoid X Receptors, said method comprising causing said process to be conducted in the presence of at least one compound as set forth in claim 7.

23. A method for modulating a process mediated by one or more Retinoid X Receptors, said method comprising administering to a mammalian subject an amount, effective to modulate said process

mediated by said one or more Retinoid X Receptors, of one or more  
ligand of claim 2.

24. A method for modulating a process mediated by one or  
more Retinoid X Receptors, said method comprising administering to  
5 a mammalian subject an amount, effective to modulate said process  
mediated by said one or more Retinoid X Receptors, of one or more  
compound of claim 5.

25. A method for treating a mammalian subject requiring  
Retinoid X Receptor therapy comprising administering to such  
10 subject a pharmaceutically effective amount of one or more ligands  
as set forth in claim 2,

26. A method for treating a mammalian subject requiring  
Retinoid X Receptor therapy comprising administering to such  
subject a pharmaceutically effective amount of one or more  
15 compounds as set forth in claim 5.

27. A method for increasing plasma concentrations of  
high density lipoprotein in a mammalian subject comprising  
administering to such subject a pharmaceutically effective amount  
of one or more ligands as set forth in claim 5.

28. A method for determining the presence of one or more  
20 Retinoid X Receptors comprising combining a compound of claim 5  
with a sample containing one or more unknown receptors and  
determining whether said ligand binds to any receptor in said  
sample.

29. A method of purifying Retinoid X Receptors comprising combining a compound as set forth in claim 5 with a sample containing one or more said Retinoid X Receptors, allowing said compound to bind with Retinoid X Receptors, and separating out  
5 the bound combination of said compound and Retinoid X Receptor.

30. A composition comprising a first ligand which selectively activates Retinoid X Receptors in preference to Retinoic Acid Receptors, in combination with a second ligand which selectively activates Retinoic Acid Receptors in preference to  
10 Retinoid X Receptors.

31. A composition comprising a first ligand which selectively activates Retinoid X Receptors in preference to Retinoic Acid Receptors, in combination with a second ligand which activates one or more intracellular receptors other than Retinoid X  
15 Receptors.

32. The composition of claim 30 or 31 wherein the physiological effect in mammals produced by said composition at a given concentration is greater than the additive effect achieved utilizing each said ligand alone at said concentration.

20 33. A pharmaceutical composition comprising in a pharmaceutically acceptable vehicle for enteral, parenteral, or topical administration a first ligand which selectively activates Retinoid X Receptors in preference to Retinoic Acid Receptors, in combination with a second ligand which selectively activates one or  
25 more intracellular receptors other than Retinoid X Receptors.

34. A pharmaceutical composition of claim 33 wherein said second ligand selectively activates Retinoic Acid Receptors in preference to Retinoid X Receptors.

35. A method for modulating a process mediated by intracellular receptors, said method comprising causing said process to be conducted in the presence of a composition comprising a first ligand which selectively activates Retinoid X Receptors in preference to Retinoic Acid Receptors, in combination with a second ligand which activates one or more intracellular receptors other than Retinoid X Receptors, and wherein the physiological effect in mammals produced by said composition at a given concentration is greater than the additive effect achieved utilizing each said ligand alone at said concentration.

36. The method of claim 35 wherein said second ligand selectively activates Retinoic Acid Receptors in preference to Retinoid X Receptors.

37. The method of claim 36 wherein said process is the *in vivo* modulation of lipid metabolism, *in vivo* modulation of skin-related processes, *in vivo* modulation of malignant cell development, *in vivo* modulation of premalignant lesions, or *in vivo* modulation of programmed cell death.

38. The method of claim 35 wherein said composition is present at a concentration at which neither said first nor second ligand would alone produce a significant therapeutic response.

39. The method of claim 35 wherein said second ligand activates peroxisome proliferator activated receptors.

40. The method of claim 35 wherein said second ligand activates Vitamin D receptors.

5           41. The method of claim 35 wherein said second ligand activates thyroid hormone receptors, HNF4 receptors, or members of the COUP family of receptors.